SHORT REPORT

Ataxia in the setting of complicated enteropathy: double jeopardy

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The differential diagnosis of subacute onset ataxia in the setting of enteropathy is wide. A 54 year old patient with a pancerebellar syndrome and known ulcerative jejunoileitis is described. Small bowel biopsy showed evidence of enteropathy associated T cell lymphoma and subsequent neuropathological analysis and immunophenotyping confirmed metastasis of this tumour to the cerebellum. The presence of anti-gliadin antibodies and MRI evidence of a more longstanding process suggested additional immunologically mediated cerebellar dysfunction. Lymphomatous involvement of the CNS is rare in patients with complicated enteropathies, and has not been previously reported to involve the cerebellar parenchyma. This diagnostic possibility should be borne in mind before attributing cerebellar dysfunction in patients with the coeliac related enteropathies to nutritional compromise or immunological dysfunction (gluten ataxia) alone.

CASE HISTORY

A 54 year old white man presented with an 8 month history of mild unsteadiness of gait and slurred speech. His symptoms had rapidly progressed over the preceding 2 months, and he was unable to stand unassisted and his speech had become unintelligible.

Three years earlier, he had developed a malabsorption syndrome, with progressive diarrhoea and weight loss. A diagnosis of non-granulomatous ulcerative jejunoileitis was made 1 year before the current presentation on the basis of negative anti-gliadin and anti-endomysial antibodies, lack of response to a gluten free diet and typical histopathological findings on jejunal biopsy. His bowel function and weight returned to normal after immunosuppression with cyclosporin A, azathioprine, and prednisolone. In retrospect he had had intermittent bouts of mild diarrhoea related to fatty or spicy foods for many years. The patient's identical twin brother was unaffected by a neurological disorder or any symptoms of malabsorption or food intolerance.

During admission to a local hospital for investigation of his neurological complaints, the patient had a spontaneous jejunal perforation, requiring laparotomy. Pathological examination of the resected segment of bowel showed a high grade T cell lymphoma. The patient was transferred to this hospital for further investigation.

On examination, there was a pancerebellar syndrome with severe dysarthria, abnormal smooth pursuit eye movements, hypermetric saccades, gaze evoked horizontal nystagmus with a downbeat component on rightward gaze, and marked axial and appendicular ataxia. There was hypotonia of all four limbs with normal strength and sensation, symmetric reflexes, and flexor plantar responses. Although there was no overt cognitive deficit on bedside examination, formal neuropsychometry disclosed a subtle impairment of frontal executive skills.

T1 weighted brain MRI demonstrated generalised cerebellar atrophy (fig 1A) and on T2 weighted sequences extensive cerebellar hyperintensity. A focal mass lesion in the left cerebellar peduncle became apparent on subsequent imaging 6 weeks later (Fig 1B) showing evidence of a localised mass effect.

Protein in CSF was increased at 2.18 g/l; no oligoclonal bands were detected. The white cell count in CSF was normal, and there was no growth from CSF culture. Cytology of CSF was clear. Nerve conduction studies were normal and a muscle biopsy did not show any ragged red fibres. Serum antineuronal antibodies were not detected by immunohistochemistry. Vitamin A, E, B1, B6, B12, and folate concentrations were normal. Genetic analysis for Friedreich's ataxia, the known SCA (spinocerebellar atrophy) mutations and the common mitochondrial mutations were negative. Repeat serum anti-gliadin antibodies were positive although anti-endomysial antibodies remained negative. The CSF was only tested for anti-endomysial antibodies, which were not detected.

Histopathology

In view of his progressive deterioration a biopsy of the cerebellar cortex was performed. The cerebellar cortex and white matter showed extensive infiltration by medium sized cells with pleomorphic nuclei and prominent nucleoli, which stained positively for CD45 (leucocyte common antigen) (fig 2). The purkinje cell layer showed a paucity of neurons. The tumour cells were positive for CD3 and TIA-1 (cytotoxic granule marker) but negative for CD20, CD5, CD8, and CD4. The appearances were consistent with a high grade T cell lymphoma. The jejunal biopsy showed a large cell lymphoma infiltrating the full thickness of the bowel wall, with tumour cells of identical cellular morphology and immunophenotype with those in the cerebellum. Review of the original jejunal biopsy taken 1 year previously did not show evidence of intestinal lymphoma: however, there were increased numbers of what are thought to be its normal cellular counterpart, the intraepithelial lymphocytes. These were CD3 and CD8 positive but negative for CD5. In this clinical context the current findings were consistent with a diagnosis of enteropathy associated T cell lymphoma (EATL).

The patient continued to deteriorate and 3 months after discharge from this hospital, and despite receiving chemotherapy, he died. One year later the patients' twin brother remained fit and well and his serum anti-gliadin and anti-endomysial antibodies continued to test negative.

DISCUSSION

Our patient developed a subacute progressive cerebellar syndrome in the setting of known ulcerative jejunoileitis and subsequent evidence of small bowel T cell lymphoma.

Abbreviations: SCA, spinocerebellar atrophy; CD45, leucocyte common antigen; TIA-1, cytotoxic granule marker; IEL, intraepithelial lymphocytes; EATL, enteropathy associated T cell lymphoma

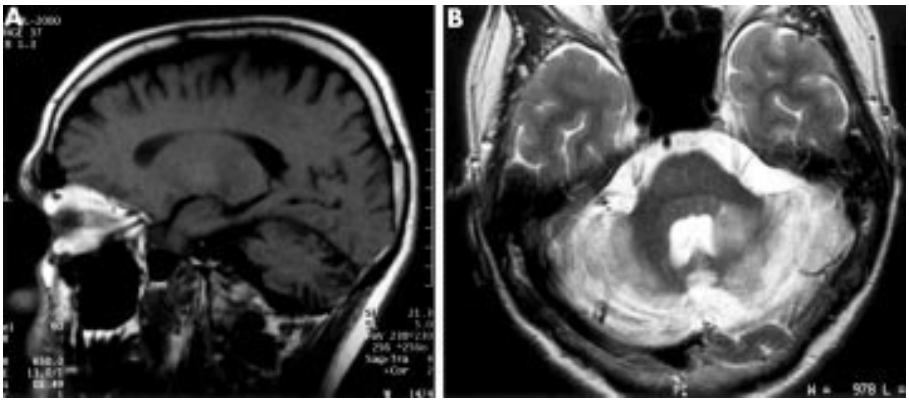

Figure 1 (A) Sagittal T1 weighted MRI showing widespread cerebellar atrophy and (B) axial T2 weighted MRI showing extensive cerebellar parenchymal high signal and a mass lesion in the left cerebellar peduncle.

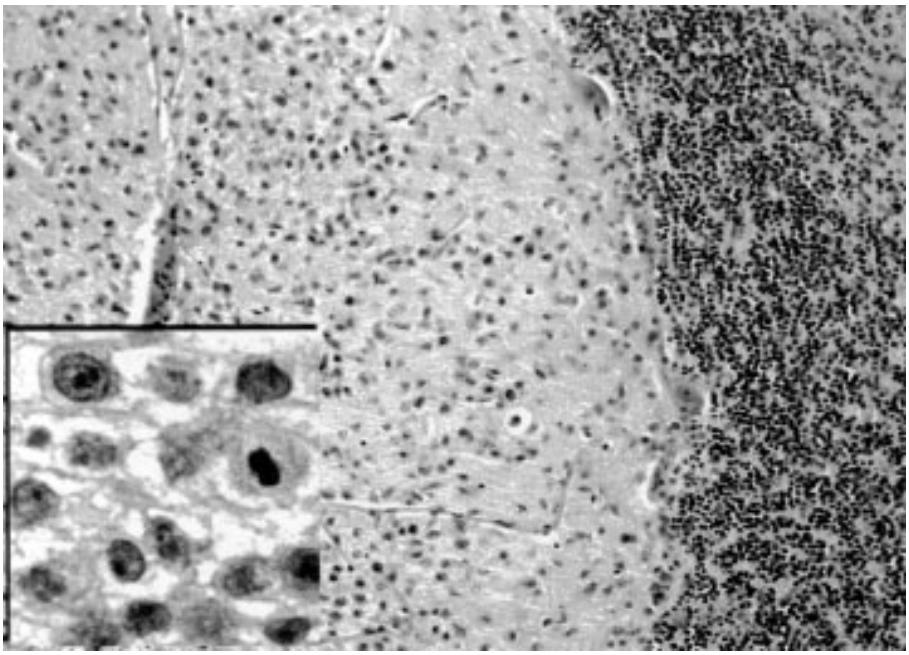

Figure 2 Photomicrograph of the cerebellum (haematoxylin and eosin stain (original magnification×100)) showing extensive infiltration of the cerebellar cortex with lymphocytes. The inset shows large atypical lymphoid cells, some of which are in mitosis (original magnification×650).

Initial diagnostic considerations included cerebellar dysfunction associated with coeliac disease (gluten ataxia), Vitamin E deficiency, a paraneoplastic cerebellar syndrome, lymphomatous involvement of the CNS, and less likely a prion disease or neurodegenerative condition.

Ataxia is the most often reported neurological manifestation of coeliac disease and may be the presenting symptom.[1] Vitamin E deficiency is occasionally found in this setting,[2] however ataxia can develop in patients with normal nutritional profiles and does not respond to vitamin supplementation.[3–5] In these patients, the neurological dysfunction is thought to be immunologically mediated, a hypothesis supported by the association with anti-gliadin antibodies. Cerebellar Purkinje cell loss, dorsal column involvement, and inflammatory cell infiltrates have been shown in cases of gluten ataxia.[6 7] In this case the presence of marked cerebellar hyperintensity on T2 weighted MRI argues against gluten ataxia as the sole aetiology, in which the cerebellum appears either normal or atrophied.[6]

Although initially diagnosed as an ulcerative jejunoileitis, repeat antigliadin antibodies in this patient proved to be positive, and interestingly recent reports suggest that coeliac disease, ulcerative jejunoileitis and EATL are closely related conditions.[8] Ulcerative jejunoileitis, a complication of coeliac disease, may precede the occurrence of overt T cell lymphoma if intestinal ulcerations contain an intraepithelial lymphocyte population that are monoclonal, or express an abnormal immunophenotype, or both.[9]

Paraneoplastic cerebellar degeneration is associated with an increasing variety of tumour types and serum antineuronal antibodies. An association with Hodgkin's disease and antibodies to Purkinje cell cytoplasm, designated anti-Tr antibodies, is well described.[10 11] There are also isolated case reports of disseminated T cell lymphoma and presumed paraneoplastic cerebellar degeneration.[12] In our case, the absence of serum antibodies to cerebellar structures and lack of oligoclonal bands in CSF, make paraneoplastic disease unlikely. Patchy cerebellar signal change is described in anti-Yo related paraneoplastic degeneration but the widespread cerebellar changes seen in our case would be atypical. The pathology of paraneoplastic cerebellar degeneration is non-specific, with variable cerebellar atrophy, neuronal loss, and inflammatory cell infiltrates.

Prion disease may present as isolated subacute ataxia[13]; however, normal EEG and imaging exclude this diagnosis. The subacute onset of disease, absence of known somatic and

mitochondrial mutations associated with ataxia, and lack of family history, do not support a diagnosis of inherited ataxia.

Cerebellar biopsy in our patient established the diagnosis of T cell lymphoma. The synchronous presentation of enteropathy associated T cell lymphoma (EATL) and CNS T cell lymphoma suggested a common lineage or shared aetiology. Moreover, lymphoma cells isolated from both bowel and brain biopsies showed identical morphology and immunophenotyping, strongly indicative of metastasis of the intestinal tumour to the cerebellum. Involvement of CNS complicating systemic lymphoma occurs in 5%-10% of patients with non-Hodgkins lymphoma, is usually B cell in origin, and involves the leptomeninges, rather than the parenchyma as in this patient.[14 15] Lymphomatous involvement of the CNS has been reported in cases of coeliac disease and in one patient with EATL.[16] In the second case, the patient had a 3 year history of coeliac disease and retrospective analysis of the original duodenal biopsy did not show evidence of a clonal T cell proliferation. To our knowledge, this is the first reported case of EATL metastasising to the cerebellar parenchyma. In addition, the presence of marked cerebellar atrophy and serum anti-gliadin antibodies provides evidence of a more longstanding process and raises the possibility of an additional immunologically mediated cerebellar syndrome in the form of "gluten ataxia" which predated the development of lymphoma.

Lymphoma in the CNS is often exquisitely sensitive to corticosteroid therapy,[17] and treatment of the patient's enteropathy may have masked or delayed the onset of his neurological symptoms which indeed developed after stopping azathioprine and a reduction in prednisone dose. An increased incidence of primary CNS lymphoma is well described in patients with immune compromise, particularly in the setting of immunosuppressive therapy.[18] There is the unlikely possibility that EATL and subsequent cerebellar metastasis in this patient developed as a result of the immunosuppression he received.

The differential diagnosis of subacute ataxia in the setting of complicated enteropathy is wide. Although lymphomatous involvement of the CNS is rare, this complication must be borne in mind, particularly in patients with known EATL presenting with a cerebellar syndrome. The diagnosis may be implied by neuroimaging and dramatic response to steroids but, as immunologically mediated cerebellar disease may be difficult to distinguish clinically in the context of the range of coeliac related disorders, histopathological confirmation is required before starting treatment.

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